Langerhans cell histiocytosis

Langerhans cell histiocytosis is a disorder in which excess immune system cells called Langerhans cells build up in the body. Langerhans cells, which help regulate the immune system, are normally found throughout the body, especially in the skin, lymph nodes, spleen, lungs, liver, and bone marrow. In Langerhans cell histiocytosis, excess immature Langerhans cells usually form tumors called granulomas. However, Langerhans cell histiocytosis is not generally considered to be a form of cancer.

In approximately 80 percent of affected individuals, one or more granulomas develop in the bones, causing pain and swelling. The granulomas, which usually occur in the skull or the long bones of the arms or legs, may cause the bone to fracture.

Granulomas also frequently occur in the skin, appearing as blisters, reddish bumps, or rashes which can be mild to severe. The pituitary gland may also be affected; this gland is located at the base of the brain and produces hormones that control many important body functions. Without hormone supplementation, affected individuals may experience delayed or absent puberty or an inability to have children (infertility). In addition, pituitary gland damage may result in the production of excessive amounts of urine (diabetes insipidus) and dysfunction of another gland called the thyroid. Thyroid dysfunction can affect the rate of chemical reactions in the body (metabolism), body temperature, skin and hair texture, and behavior.

In 15 to 20 percent of cases, Langerhans cell histiocytosis affects the lungs, liver, or blood-forming (hematopoietic) system; damage to these organs and tissues may be life-threatening. Lung involvement, which appears as swelling of the small airways (bronchioles) and blood vessels of the lungs, results in stiffening of the lung tissue, breathing problems, and increased risk of infection. Hematopoietic involvement, which occurs when the Langerhans cells crowd out blood-forming cells in the bone marrow, leads to a general reduction in the number of blood cells (pancytopenia). Pancytopenia results in fatigue due to low numbers of red blood cells (anemia), frequent infections due to low numbers of white blood cells (neutropenia), and clotting problems due to low numbers of platelets (thrombocytopenia).

Other signs and symptoms that may occur in Langerhans cell histiocytosis, depending on which organs and tissues have Langerhans cell deposits, include swollen lymph nodes, abdominal pain, yellowing of the skin and whites of the eyes (jaundice), delayed puberty, protruding eyes, dizziness, irritability, and seizures. About 1 in 50 affected individuals experience deterioration of neurological function (neurodegeneration).

Langerhans cell histiocytosis is often diagnosed in childhood, usually between ages 2 and 3, but can appear at any age. Most individuals with adult-onset Langerhans cell

histiocytosis are current or past smokers; in about two-thirds of adult-onset cases the disorder affects only the lungs.

The severity of Langerhans cell histiocytosis, and its signs and symptoms, vary widely among affected individuals. Certain presentations or forms of the disorder were formerly considered to be separate diseases. Older names that were sometimes used for forms of Langerhans cell histiocytosis include eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease.

In many people with Langerhans cell histiocytosis, the disorder eventually goes away with appropriate treatment. It may even disappear on its own, especially if the disease occurs only in the skin. However, some complications of the condition, such as diabetes insipidus or other effects of tissue and organ damage, may be permanent.

Frequency

Langerhans cell histiocytosis is a rare disorder. Its prevalence is estimated at 1 to 2 in 100,000 people.

Genetic Changes

Somatic mutations in the *BRAF* gene have been identified in the Langerhans cells of about half of individuals with Langerhans cell histiocytosis. Somatic gene mutations are acquired during a person's lifetime and are present only in certain cells. These changes are not inherited.

The *BRAF* gene provides instructions for making a protein that is normally switched on and off in response to signals that control cell growth and development. Somatic mutations cause the BRAF protein in affected cells to be continuously active and to transmit messages to the nucleus even in the absence of these chemical signals. The overactive protein may contribute to the development of Langerhans cell histiocytosis by allowing the Langerhans cells to grow and divide uncontrollably.

Changes in other genes have also been identified in the Langerhans cells of some individuals with Langerhans cell histiocytosis. Some researchers believe that additional factors, such as viral infections and environmental toxins, may also influence the development of this complex disorder.

Inheritance Pattern

Langerhans cell histiocytosis is usually not inherited and typically occurs in people with no history of the disorder in their family.

A few families with multiple cases of Langerhans cell histiocytosis have been identified, but the inheritance pattern is unknown.

Other Names for This Condition

- Hashimoto-Pritzger disease
- histiocytosis X
- Langerhans cell granulomatosis
- LCH

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Langerhans cell histiocytosis, multifocal
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0019621/

Other Diagnosis and Management Resources

- Cincinnati Children's Hospital Medical Center
  https://www.cincinnatichildrens.org/health/l/langerhans-cell-histiocytosis-lch
- Cleveland Clinic
  http://my.clevelandclinic.org/childrens-hospital/health-info/diseases-conditions/langerhans-cell-histiocytosis
- National Cancer Institute: Langerhans Cell Histiocytosis Treatment
  https://www.cancer.gov/types/langerhans/patient/langerhans-treatment-pdq
- Seattle Children's Hospital
  http://www.seattlechildrens.org/medical-conditions/heart-blood-conditions/langerhans-cell-histiocytosis/
- St. Jude Children's Research Hospital
  https://www.stjude.org/disease/langerhans-cell-histiocytosis.html?vgnextoid=d1d067f714773210VgnVCM1000001e0215acRCRD&vgnextchannel=bc4fbfe82e118010VgnVCM1000000e2015acRCRD
- Sydney Children's Hospital
  http://www.kids-cancer.org/cancer-blood-disorders/what-is-cancer/langerhans-cell-histiocytosis.aspx

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html

- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Histiocytosis
  https://medlineplus.gov/ency/article/000068.htm
- Health Topic: Immune System and Disorders
  https://medlineplus.gov/immunesystemanddisorders.html
- Health Topic: Interstitial Lung Diseases
  https://medlineplus.gov/interstitiallungdiseases.html

Genetic and Rare Diseases Information Center

- Langerhans cell histiocytosis
  https://rarediseases.info.nih.gov/diseases/6858/langerhans-cell-histiocytosis

Additional NIH Resources

- National Cancer Institute: Langerhans Cell Histiocytosis Treatment
  https://www.cancer.gov/types/langerhans/patient/langerhans-treatment-pdq

Educational Resources

- Disease InfoSearch: Langerhans cell histiocytosis
  http://www.diseaseinfosearch.org/Langerhans+cell+histiocytosis/4086
- MalaCards: langerhans-cell histiocytosis
  http://www.malacards.org/card/langerhans_cell_histiocytosis
- Orphanet: Langerhans cell histiocytosis
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=389

Patient Support and Advocacy Resources

- American Lung Association
  http://www.lung.org/
- Histio UK
  http://www.histiouk.org/

- Histiocytosis Association of America
  https://www.histio.org/
- National Organization for Rare Disorders
  https://rarediseases.org/rare-diseases/langerhans-cell-histiocytosis/

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22Langerhans+cell+histiocytosis%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Histiocytosis,+Langerhans-Cell%5BMAJR%5D%29+AND+%28Langerhans+cell+histiocytosis%5BTI%5D%29+AND+review%5Bpt%5D+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- LANGERHANS CELL HISTIOCYTOSIS
  http://omim.org/entry/604856

Sources for This Summary

- Abla O, Egeler RM, Weitzman S. Langerhans cell histiocytosis: Current concepts and treatments. Cancer Treat Rev. 2010 Jun;36(4):354-9. doi: 10.1016/j.ctrv.2010.02.012. Epub 2010 Feb 25. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20188480
- Badalian-Very G, Vergilio JA, Degar BA, MacConaill LE, Brandner B, Calicchio ML, Kuo FC, Ligon AH, Stevenson KE, Kehoe SM, Garraway LA, Hahn WC, Meyerson M, Fleming MD, Rollins BJ. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010 Sep 16;116(11):1919-23. doi: 10.1182/blood-2010-04-279083. Epub 2010 Jun 2.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20519626
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3173987/
- Brown NA, Furtado LV, Betz BL, Kiel MJ, Weigelin HC, Lim MS, Elenitoba-Johnson KS. High prevalence of somatic MAP2K1 mutations in BRAF V600E-negative Langerhans cell histiocytosis. Blood. 2014 Sep 4;124(10):1655-8. doi: 10.1182/blood-2014-05-577361. Epub 2014 Jun 30.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/24982505
- Chakraborty R, Hampton OA, Shen X, Simko SJ, Shih A, Abhyankar H, Lim KP, Covington KR, Trevino L, Dewal N, Muzny DM, Doddapaneni H, Hu J, Wang L, Lupo PJ, Hicks MJ, Bonilla DL, Dwyer KC, Berres ML, Poulikakos PI, Merad M, McClain KL, Wheeler DA, Allen CE, Parsons DW. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. Blood. 2014 Nov 6;124(19):3007-15. doi: 10.1182/blood-2014-05-577825. Epub 2014 Sep 8.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25202140
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4224195/

- Donadieu J, Chalard F, Jeziorski E. Medical management of langerhans cell histiocytosis from diagnosis to treatment. Expert Opin Pharmacother. 2012 Jun;13(9):1309-22. doi: 10.1517/14656566.2012.688028. Epub 2012 May 11. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22578036
- El Demellawy D, Young JL, de Nanassy J, Chernetsova E, Nasr A. Langerhans cell histiocytosis: a comprehensive review. Pathology. 2015 Jun;47(4):294-301. doi: 10.1097/PAT.0000000000000256. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25938350
- Grana N. Langerhans cell histiocytosis. Cancer Control. 2014 Oct;21(4):328-34. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25310214
- Nelson DS, van Halteren A, Quispel WT, van den Bos C, Bovée JV, Patel B, Badalian-Very G, van Hummelen P, Ducar M, Lin L, MacConaill LE, Egeler RM, Rollins BJ. MAP2K1 and MAP3K1 mutations in Langerhans cell histiocytosis. Genes Chromosomes Cancer. 2015 Jun;54(6):361-8. doi: 10.1002/gcc.22247. Epub 2015 Mar 31.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25899310
- Park L, Schiltz C, Korman N. Langerhans cell histiocytosis. J Cutan Med Surg. 2012 Jan-Feb;16(1): 45-9. Review.
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22417995
- Satoh T, Smith A, Sarde A, Lu HC, Mian S, Trouillet C, Mufti G, Emile JF, Fraternali F, Donadieu J, Geissmann F. B-RAF mutant alleles associated with Langerhans cell histiocytosis, a granulomatous pediatric disease. PLoS One. 2012;7(4):e33891. doi: 10.1371/journal.pone.0033891. Epub 2012 Apr 10. Erratum in: PLoS One. 2012;7(6). doi:10.1371/annotation/74a67f4e-a536-4b3f-a350-9a4c1e6bebbd. Mian, Sophie [corrected to Mian, Syed].
  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22506009
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3323620/

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/langerhans-cell-histiocytosis

Reviewed: June 2015
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
U.S. National Library of Medicine
National Institutes of Health
Department of Health & Human Services